

Extrapolation from Occupational Studies: A Substitute for Environmental Epidemiology

by Philip E. Enterline*

Extrapolation from occupational data to general environmental exposures gives some interesting results, and these results might be useful in our decision-making process. These results could never be observed by environmental epidemiology and this method probably represents the only way of quantifying the health effects of low-exposure levels.

Three linear models for extrapolating to low levels are presented—one from Canadian data, one from American data and one from British data. One or more of these is applied to two recently publicized asbestos exposures: exposures resulting from asbestos heat shields in hair dryers and exposures in public school buildings. Predictions are derived as to the effects of asbestos exposures on cancer mortality. A comparison is made between predictions made on the basis of a linear and nonlinear model.

There has been conflicting evidence of effects of environmental pollution on the occurrence of chronic disease, and in particular cancer. There have been striking acute effects of single episodes of air pollution, however, in the Meuse Valley, Belgium, Donora, Pa., and London, England and this has served to focus attention on the problem of environmental pollution (1-3). Repeated acute health effects have also been observed in time series studies of mortality in New York City, in the New York-New Jersey metropolitan area, and in Pittsburgh, Pa. (4-6).

The problems in detecting chronic effects of air pollution are mainly those of very small doses in the presence of many confounding variables and the long period of time required for chronic disease to become manifest. It seems unlikely that these problems can be easily solved. To many, ecologic correlations seem to have the potential for a solution, however these are unreliable and have, in my opinion, told us very little.

One way to estimate the health effects of specific contaminants in the general environment is to find

some environment where doses can be measured and are sufficiently large to overwhelm the confounding effects of uncontrollable or unknown variables, and from studies of the effects of such environments on human health extrapolate to low dose levels. Such an environment is often present in occupational settings, and I will present two case histories where extrapolation from occupational studies presents an apparent answer to what appears to be an otherwise unsolvable problem. In doing this I can also illustrate some difficulties and some necessary assumptions.

Last summer we heard a great deal about the cancer-producing potential of hand-held dryers. As you may recall, the question was raised when a photographer for a Washington, D.C., TV station was drying photographic film with a hair dryer and noticed some specks on the film. This led to an investigation resulting in the finding that asbestos was emitted from hair dryers containing asbestos insulating heat shields, and shortly thereafter to the replacement or reworking of a large proportion of such dryers in the U.S. This action took place before there was any serious attempt to estimate the extent of the health hazard caused by asbestos released by hair dryers.

The hair dryers definitely released asbestos.

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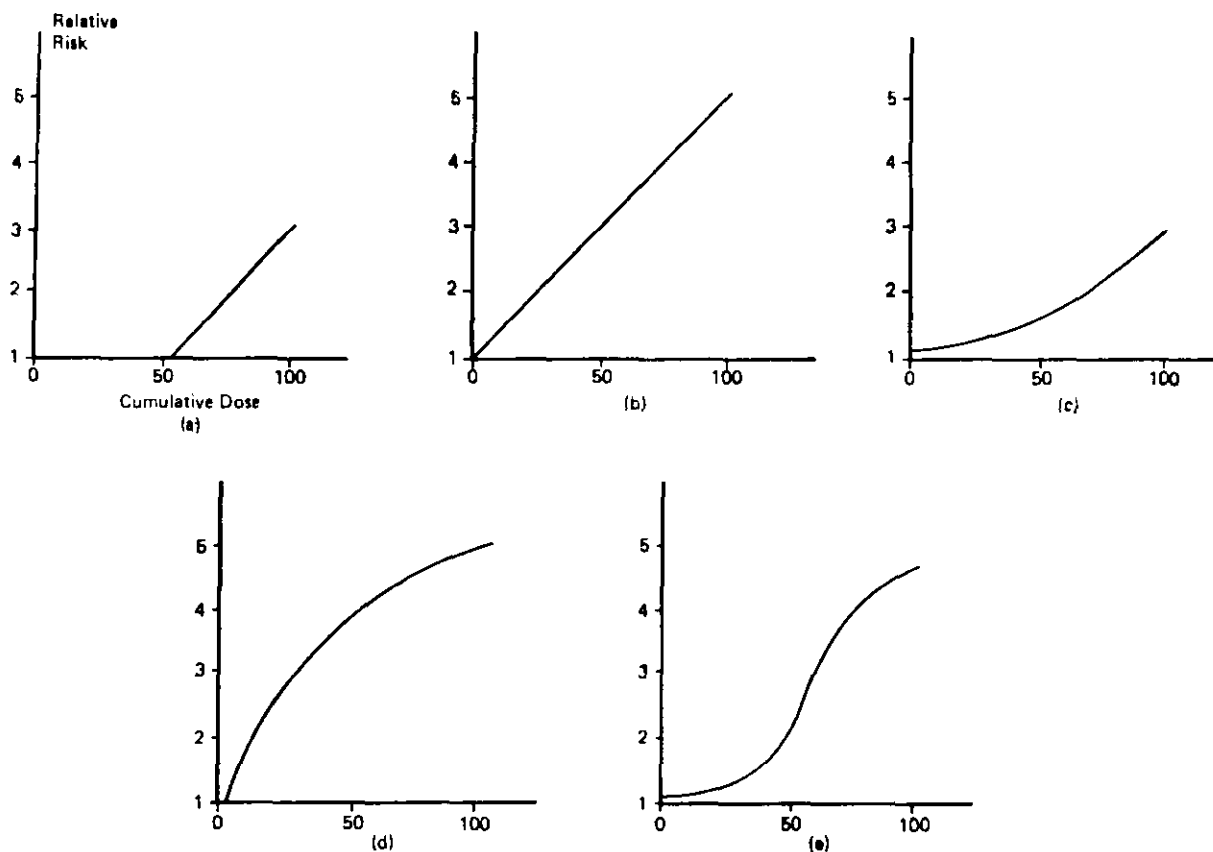


FIGURE 1. Diagrammatic representation of various different relationships between response and dose: (a) threshold; (b) (recti)linear; (c) quadratic; (d) sublinear; (e) cumulative normal.

Test results obtained by NIOSH on hand-held hair dryers showed up to 0.034 fibers of all sizes per cubic centimeter in the air stream (7). The average based on several tests appears to be 0.0072 asbestos fibers. These data can be translated into an incremental concentration of airborne asbestos fiber in room air if certain assumptions about the use of hair dryers can be made. If a hair dryer is used 15 min each day in a room containing 18 m^3 of space and having 12 air turnovers per day and 50% replacement per turnover, then it can be estimated that in the long run the increment to room air in terms of asbestos fiber per cubic centimeter is 0.00074. This relates to fibers of all sizes. Converting to fibers greater than $5 \mu\text{m}$ in length by dividing by 20 gives a concentration of 0.000037 fibers/cc.* The occupational standard for asbestos fiber is 2 fibers/cc greater than $5 \mu\text{m}$ in length. What then are the health effects of asbestos fiber at this very low concentration (1)?

It would be impossible to ever design an envi-

ronmental epidemiologic study which would measure the health effects of airborne asbestos at levels as low as 0.000037 fibers/cc. If fact it is unlikely that the effects of exposure at 1 fiber/cc can be reliably detected—a level almost 30,000 times higher. However, one way to estimate very low level effects would be to find an effect at a much higher level and extrapolate to zero or to very low levels. To do this, of course, requires assurance that a dose-response relationship exists and knowledge of just what form this relationship takes, in particular, knowledge as whether there is a threshold below which no response occurs.

Figure 1 is taken from the recent report of the British Advisory Committee on Asbestos and shows some forms such a relationship could take (8). Only the upper left-hand corner relationship shows a clear threshold, although the two right-hand curves have been interpreted by some as representing a kind of threshold. The simple linear relationship which appears at the top center is the one most commonly assumed. It is popular with government scientists and decision makers since it may overstate response at very low levels and thus might

*A conversion factor of 20 appears to be conservative. EPA uses 200 in its water quality document.

best serve to protect the public. Some call such probably overstated estimates "conservative," since they offer maximum protection from environmental contaminants. For a carcinogen this is also sometimes referred to as a one-hit model, on the grounds that it represents the outcome of a disease producing interaction between a single molecule of a carcinogen and a single human cell, so that response is directly proportional to the amount of the carcinogen present. At low dose levels the choice seems to be between the two upper right hand curves. There is animal evidence which will support either. The curvilinear relationship is one I've been interested in and could result from the kind of inverse relationship between dose rate and time to tumor proposed by Druckey (9). One variant of the upper right-hand curve is the so-called "hockey stick" relationship. This consists of two straight lines—one with a very shallow slope at low dose levels, and one with a much steeper slope at higher dose levels.

There are two studies of asbestos exposed workers in which the relationship between asbestos exposure at several levels and respiratory cancer mortality have been reported: a Canadian study of miners and millers in Quebec Province and an American study of asbestos products workers (10, 11). In both of these studies there is a strong relationship between a time-weighted measure of dose and respiratory cancer mortality in the range of asbestos dust exposures commonly encountered in the past by workers engaged in the mining, milling and processing of asbestos. In addition to showing clearly that a dose-response relationship exists, these studies provide information on both the form and the strength of the relationship. Extrapolation to low levels of asbestos exposure is possible from these studies if the relationship at high dose levels can be extended to doses near zero.

Dose-response data from these studies are shown in Figure 2 (8). Here the American study has been divided into two segments: a group of maintenance and service workers exposed intermittently to asbestos and a group of production workers exposed more or less continuously. A linear dose-response curve has been fitted free hand to all three sets of data. The fit is clearly best for the Canadian data (Quebec miners and mill workers), but less good for the American data sets. Numbers of workers involved in the American study are considerably smaller than in the Canadian study, however, and this could account for some of the variability in the American data. Clearly, the Canadian study shows a considerably shallower slope and a much weaker respiratory cancer re-

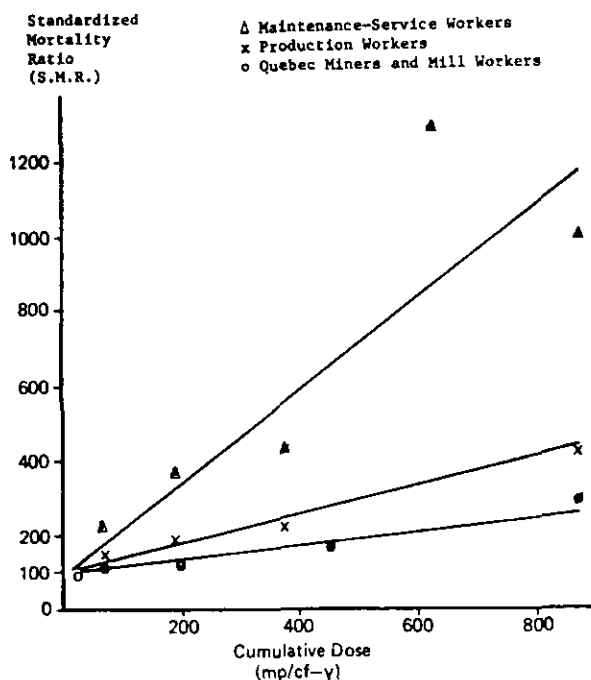


FIGURE 2. Dose responses for lung cancer with freehand lines drawn.

sponse than the American study. In addition to these two studies, there is one British study where a single point can be plotted (12): that is, a worker population reported at a single dose level in relation to a demonstrated respiratory cancer excess. From this point a linear extrapolation can be made to zero.

Figure 3 shows more recent dose-response data from the American study and shows a mathematically fitted linear regression line (13). Here the maintenance-service workers have been grouped with the production workers due to the small numbers problem. The linear regression line is a better fit than before and is probably a pretty good description of the data at these very high exposure levels. Interestingly, the regression line did not need to be forced through the origin for this data set. The y intercept is actually 100, as shown.

In order to use these data from occupational studies to estimate the effect of continuous exposures in the general population it is necessary to convert 8-hr, 5 day week exposure to 24-hr, 7 day week exposure. One way to do this is to assume that the important thing about exposure is how much is received, rather than how it is received. That is, to assume that an 8-hr exposure at some level is equivalent in its health effects to a 24-hr exposure at a third of that level; and a 5 day/week exposure at some level is equivalent in its health effects to 5/7 of that level for a 7 day week. If

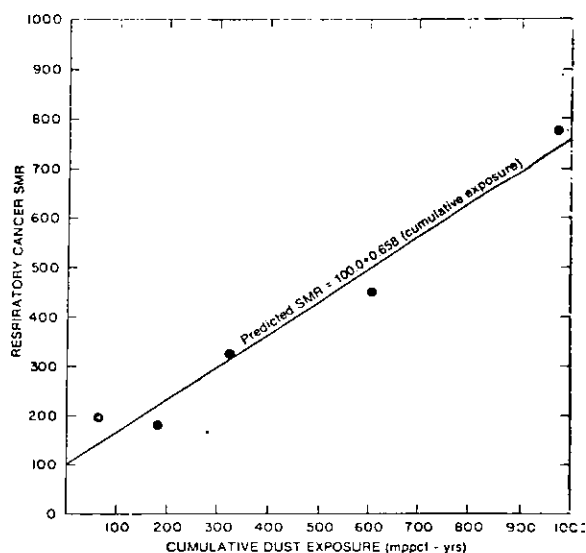


FIGURE 3. Asbestos dust exposure and respiratory cancer mortality.

these assumptions can be made, an 8-hr day, 5 day/week dose can be converted to a continuous dose by multiplying by $(8/24)(5/7) = 0.24$.

Table 1 shows the linear regression coefficients for all three occupational studies for both 8 hr, 5 day week doses and continuous exposure. I have forced the origin of the regression line for the Canadian study through zero. Since only one data point was available for the British study, the origin is shown through zero. To illustrate how data in Table 1 were derived, the linear regression equation shown in Figure 3 is:

$$\text{SMR} = 100.0 + 0.658 (\text{mmpcf-years})$$

This was converted to fibers/cc-years $> 5 \mu\text{m}$ in length by dividing by 3 (2):†

$$\text{SMR} = 100.0 + 0.219 (\text{fibers/cc-yr})$$

SMR's were then converted to lung cancer deaths per million exposed by assuming that an

†Since the historic method of measuring asbestos exposure was million particles per cubic foot (mppf) in the Canadian and American studies, it was necessary to convert this to the modern method of fibers $5 \mu\text{m}$ in length per cubic centimeter. The conversion used was to divide by 3, under the assumption that $1 \text{ mmpcf} = 3 \text{ f/cc}$. In a report by the British Advisory Committee on Asbestos, conversion factors of 1, 2 and 5 f/cc per 1 mppcf were used. The Canadian Beaudry Commission used 3 to 7, while in EPA's water criterion document (1979) 6 f/cc per 1 mppcf was used. The most conservative estimate of response at low doses in terms of protecting the public would result from assuming a low conversion factor.

Table 1. Linear regression coefficients for asbestos exposure and lung cancer derived from three occupational studies by type of exposure.

Study	Fibers/cc $> 5 \mu\text{m}$ in length	
	8 hr/day, 5 days/week	Continuous exposure
Canadian	31.2	131.2
American	109.6	460.5
British	250.0	1050.0

Table 2. Estimated incremental lung cancer deaths in 70 years per million exposed resulting from use of hair dryers.

Study	Fibers/cc $> 5 \mu\text{m}$ in length	
	8 hr/day, 5 days/week	Continuous exposure
Canadian	0.06	0.24
American	0.20	0.85
British	0.46	1.94

expected 5% of future deaths or 50,000 expected deaths per million will be due to lung cancer. Thus the SMR (lung cancer deaths per 100 deaths expected) can be converted to lung cancer deaths per 50,000 expected by multiplying by 500. The regression equation then becomes:

Lung cancer deaths per 50,000 expected (or one million exposed) = $50,000 + 109.6 (\text{f/cc-years})$

We are only interested here in incremental lung cancer deaths, and information about this is contained in the regression coefficient (109.6). When multiplied by dose this gives incremental lung cancer cases per million exposed. For example, this equation provides an estimate that one year's exposure at 1 fiber/cc for 8 hr/day, 5 days/week would result in 109 cases per million exposed. Exposure at 2 fibers/cc for 50 years would result in 10,900 cases per million exposed. For continuous exposure the regression coefficient for 8 hr/day, 5 days/week needs to be divided by 0.24.

As noted above, hand-held hair dryers used repeatedly may increase airborne concentrations of asbestos in a small enclosed area by 0.000037 fiber/cc. Since life expectancy at birth is about 70 years and incremental effects of asbestos exposure would not appear until after about 20 years, (and the three studies upon which the models are based took this into consideration) the effective time-weighted exposure for someone living all his life in such a small enclosed area would be: $(0.000037)(50) = 0.00185 \text{ fibers/cc-years}$. Table 2 shows for each of the three models the incremental effects of exposures to asbestos resulting from the lifetime use of a hand-held hair dryer for 15 min each day

and living all the time in the small room were it is used. Also shown are the corresponding deaths if exposure were 8 hr/day, 5 days/week, as in an occupational exposure.

We might add to the above other cancers associated with asbestos in addition to lung cancer. These include pleural and peritoneal mesothelioma, gastrointestinal cancers, and laryngeal cancer. In studies to date, it appears that for every two lung cancers caused by asbestos, one of these other cancers appears. The lifetime effect of hand-held hair dryers would be, therefore, 0.36, 1.27 and 2.91 cancers per million users based on the Canadian, the American and the British models, respectively.

All this projects what would happen if hand-held hair dryers were to continue to be made with asbestos. We can also project what would have happened if hair dryers had not been recalled (or the recall was ineffective) but the use of asbestos in their manufacture was discontinued. At the same time the recall decision was made, hand-held hair dryers in use had a remaining life expectancy of about 5 years and since no more hair dryers were to be sold containing asbestos, exposure would be greatly shortened and the numbers of cancers per million users would be only 1/10 of the above, that is, 0.03, 0.12 and 0.29 cancers per million users. Moreover, if the user of the hair dryer was not in the room where he or she used the hair dryer—say two thirds of the time—the risk approaches 1 per 100 million users. Whether this calculation would have made any difference in the decision to publicize the hair dryer problem is not certain. Whatever amount of panic, worry or tendency to encourage future disbelief of alleged cancer hazards on the part of the general public a recall would have caused should certainly have been weighed against whatever benefits these calculations imply would accrue from the withdrawal.

This type of calculation can be extended to an environmental problem of current concern, and that is the problem of asbestos in public school buildings. To place the hair dryer incident in perspective, it must be pointed out that in cities the airborne asbestos fiber concentration averages 5 ng/m³ and is as high as 50 ng/m³. The increment added in a small room by daily use of a hand-held hair dryer is about 1 ng/m³. Its effect on much larger areas and on the general environment would, of course, be imperceptible.

There are 60 million children enrolled in schools in the United States in 107,000 schools. It is estimated that at least 5 to 15% of the school buildings contain asbestos. For schools with the asbestos in good condition and tightly bound, the level of asbestos exposure appears to be no different than the level in ambient air. However where the asbestos installation is visibly worn or damaged it is estimated (14) that exposures can approach 500 ng/m³. Where the asbestos is abused, or torn or struck, very high exposures can occur—possibly as high as 50,000 ng/m³.

Estimates of the cancer deaths that might result from exposure of school children at various levels of asbestos can be made from our experience in occupational settings, except that the analogy is better since time in school buildings approximates time at work. Thus there is no need to adjust 8 hour a day 5 day a week exposures to continuous exposure.

Table 3 shows the effect of lifetime exposure at five levels and under two different sets of assumptions about the shape of the dose-response curve. I have assumed, as before, that a lifetime is 70 years and that cancer starts to appear after 20 years. The highest exposure level shown is the level currently allowed for workers in industry. A lifetime exposure at the level that exists in some schools with deteriorating asbestos is estimated to produce up to 110 deaths per million exposed.

Table 3. Incremental lung cancer deaths in 70 years per million exposed resulting from various levels of asbestos exposure, American linear model and curvilinear model.

Level of exposure, ng/m ³	Equivalent fibers/cc (> 5 μ m long)	Lung cancer deaths		
		American linear model		Curvilinear model ^a
		8 hr/day 5 days/week	Continuous exposure	
1	0.000037	0.20	0.85	—
5	0.0002	1.09	4.60	—
50	0.002	10.96	46.06	—
500	0.02	109.60	460.60	1
5,000	0.2	1,096.00	4,606.00	50
50,000	2.0	10,960.00	46,060.00	5,000

^a60 years continuous exposure.

Where asbestos in schools is mechanically disturbed, however, the effects could be as in occupational environments. Of course, most of us do not spend this lifetime in school, and actual exposure should be reduced proportionately. The effects of exposures depend, of course, on the model used. I have used the American linear model but have also introduced an alternative model which incorporates two additional ideas: that the time between exposure and the appearance of cancer is longer at lower doses than at higher doses, and that the population is highly heterogeneous in terms of susceptibility (15). This gives a curvilinear dose-response curve with relatively little response at lower levels. The time to tumor assumption is clearly supported in animal experiments, but we have little data on humans to support it. I have no doubts about the second assumption. The variability in human response is one of the most striking features of studies of occupational exposures. Clearly this change from a linear to a nonlinear dose-response curve makes a big difference, particularly at the lower dose levels. This illustrates the importance of good information on how a carcinogen really works and on the shape of the dose-response curve.

Clearly the school building problem is more important than the hair dryer problem. In fact the hair dryer problem probably wasn't a problem.

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